REMARKS

Claims 1-16 are pending in this application. Claims 3, 4 and 10-16 are canceled without prejudice or disclaimer, and claims 1, 5, 6 and 9 are amended herein. Upon entry of this amendment, claims 1, 2 and 5-9 will be pending. Entry of this amendment and reconsideration of the rejections are respectfully requested.

No new matter has been introduced by this Amendment. Support for the amendments to the claims is as follows. Claim 1 has been amended to incorporate the limitations of claims 8 and 4, and also to amend the recitation that the first and second antibodies are adsorbed on a carrier to "wherein the first antibody and second antibody are adsorbed on a carrier, or wherein the first antibody is adsorbed on a carrier and the second antibody is adsorbed on a carrier dispersed in a solution or is dissolved in a solution." Support for this recitation may be found in the specification on page 20, at bottom, to page 21, line 26, and in claim 8. Claim 9 has similarly been amended to incorporate the limitations of claims 10 and 11.

Claims 1-11 and 13-16 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while possible of being enabling for the Trk49 and Trk62 antibodies, does not reasonably provide enablement for the scope of antibodies as claimed or even for other antibodies specific for the 5a and 5b isoforms of tartrate resistant acid phosphatase. (Office action p. 2)

The Examiner states that the specification does not provide enablement for the claimed scope of antibodies. Claim 1 recites a method using two types of antibodies, which are defined by affinity properties (i) to (iv).

Reconsideration of the rejection is respectfully requested in view of the amendments to the claims.

The issue raised by the Examiner is whether the specification enables one of skill in the art to obtain the full scope of antibodies encompassed by this definition.

In this regard, Applicant first notes that claim 1 is not claiming the antibodies themselves, but is claiming a method using antibodies. That is, in effect, the antibodies are tools in the method. The Examiner states at the bottom of page 3, that "an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*," an argument which is clearly directed to claiming a large genus of products with possibly different characteristics. This is not the case in the present claims.

On the top of page 3 of the Office action, the Examiner refers to "the definition of target/competitor pairs ..." and refers on page 3, line 5, to "Unpredictable experimentation [sic] to define target/competitor pairs and appropriate specific antibodies ... unguided by applicant's disclosure, would be required for one to predictably practice the invention with other than the 5a and 5b isoforms of tartrate resistant acid phosphatase and fragments thereof."

In response, Applicant submits that no "undue experimentation" (i.e., *Wands* factor (H)) is necessary in order to practice amended claim 1. In particular, claim 1 has been amended to recite the limitation of former claim 2 (revised for clarity) that: "the target substance is an intact enzyme having an enzymatic activity." The identification of enzymes as target substances and the obtaining of antibodies against enzymes is well known in the art. In the method of claim 1, a target substance and a competitive substance in a sample are bonded to the first and second antibodies adsorbed on a carrier (or wherein the first antibody is adsorbed on a carrier and the second antibody is adsorbed on a carrier in a solution or is dissolved in a solution), and the level of the bonded target substance is assayed. This method, in itself, is straightforward, and can be easily carried out by one of skill in the art.

Applicant also notes the Examiner's arguments on page 3, lines 9 and ff., of the Office action, including the Examiner's arguments with regard to Janckila and the "difficulties in eliciting monoclonal antibodies to the isoforms of tartrate resistant acid phosphatase." However, alleged "difficulty" in obtaining a particular antibody in the prior art is not, in itself, a proper argument that the present method is not enabled. Applicant submits that one of skill in the art could obtain antibodies meeting the limitations in the claims, for use in the method of claim 1.

Applicant also notes the Examiner's comments with regard to "predictably [practicing] the method" (page 3, last 8 lines). The Examiner appears to be stating that other antibodies than Trk49 and Trk62, once obtained, would not necessarily "work" in the method, and undue experimentation would be necessary to obtain the appropriate antibodies. The Examiner appears be arguing only that

the method of the invention, carried out in other systems than explicitly disclosed in the specification, might not "work perfectly." However, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect" (see *CFMT Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003), discussed in MPEP 2164). The claimed method could be practiced by one of skill in the art and a result obtained. The Examiner's arguments appear to be improper arguments for lack of enablement.

In addition, Applicant submits that the experimental details in the specification regarding the working examples of the Trk49 and Trk62 antibodies can be readily applied to other systems within the scope of claim 1 by one of skill in the art. Reconsideration of the rejection is respectfully requested.

Claims 1-11 and 13-16 are further rejected under 35 U.S.C. §112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure. (Office action p. 4)

This rejection is respectfully traversed, and reconsideration of the rejection is requested for the pending claims.

The Examiner states that "the specification does not provide evidence that the required biological materials are ... deposited in compliance with the criteria set forth in 37 CFR 1.801-

1.809." The Examiner refers specifically to "cell lines which produce antibodies having the exact chemical identity and properties of the antibodies designated Trk49 and Trk62."

However, the hybridomas for Trk62 and Trk49 **were** deposited in the Patented Organism Deposition Center (see page 18, line 25, to page 19, line 5, of the specification). This depository is an acceptable International Depository Authority under the Budapest treaty, according to MPEP 2405. The specification does specifically identify the biological material by the receipt numbers, and Applicant submits that this provides proper written description (see MPEP 2406.01).

Claims 1-11 and 13-16 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. (Office action p. 5)

Reconsideration of the rejection is respectfully requested in view of the amendments to the claims.

a) The Examiner refers to the word "using." Claim 1 has been amended to replace "using the two types of antibodies" with --providing a first antibody and a second antibody-- .

b) The Examiner states that "the use" and "the level" lack antecedent basis.

The term "the use of two types of antibodies" occurs in the preamble to claim 1. This portion of the rejection is respectfully traversed. This phrase, as used in the preamble to claim 1, is clearly part of a general characterization of the method that is to follow, and does not require an antecedent.

The phrase "the level of the bonded target substance" appears in the last clause of original claim 1. This phrase also requires no antecedent, because there is **inherently** one "level" (that is, value of the amount) of the target substance, and the definite article "the" is appropriate. (See MPEP 2173.05(e)).

c) The Examiner states that the preambles to claims 2-8 and 13-16 should begin with the definite article "the" instead of "a." This rejection is moot for claims 2-4 and 13-16, which have been canceled without prejudice or disclaimer, and is traversed for claims 5-8. It is generally acceptable for dependent claims to begin with the indefinite article "A" (see the multiple dependent claim examples in MPEP 608.01(n)).

d) The Examiner states that in claim 3, "the enzymatic activity" lacks antecedent basis. For clarity, claim 1 has been amended to recite "an intact enzyme having an enzymatic activity." However, Applicant also notes that intact enzymes inherently have enzymatic activity (see MPEP 2173.05(e)).

e) The Examiner states that in claim 8, the interrelationships of the components are not clear, in particular how "dissolved" further limits "adsorbed on a carrier." This portion of the rejection is respectfully traversed. In claim 8, the second antibody is "adsorbed on a carrier dispersed in a solution **or** is dissolved." It is clear from the conjunction "or" that this recites two alternatives for the second antibody: 1) adsorbed on a carrier dispersed in a solution; or 2) dissolved. The word "dissolved" is not limiting "adsorbed on a carrier."

f) The Examiner refers to "the use of two types of antibodies" in the preamble. This portion of the rejection is respectfully traversed. The preamble is simply generally summarizing the method that is to follow.

g) The Examiner refers to "dissolved" in claim 11. This portion of the rejection is respectfuly traversed, analogously to point (e) above.

Claims 1, 2, and 7-11 are rejected under 35 U.S.C. §102(b) as being clearly anticipated by Furie et al. (U.S. 4,769,320). (Office action p. 7)

Reconsideration of the rejection is respectfully requested for the pending claims.

The Examiner states that Furie's method involving two antibodies "with specificity and selectivity for each of an abnormal human prothrombin with reduced enzymatic activity and native human prothrombin, for immunoassay of the two forms of prothrombin present in the same sample" meets the limitations of the claims.

However, Applicant submits that Furie's antibodies do **not** meet limitations (i) and (iv) of the first and second antibody as recited in amended claim 1, or in the kit of claim 9.

With regard to limitation (i), Furie states in column 6, line 10: "Anti-prothrombin-Ca(II) binds tightly to prothrombin in the presence of calcium, but interacts **minimally** with abnormal prothrombin" (emphasis added). Therefore, this antibody does not meet this limitation of claim 1,

which recites: "the first antibody **has affinity for** the target substance **and** the competitive substance."

With regard to limitation (iv) in claim 1, there is no specific disclosure as to whether Furie's "anti-native prothrombin" or "anti-abnormal prothrombin" has the higher affinity to its respective binding partner.

Further, in the assay of Furie et al, the antibodies are only **individually** adsorbed on carriers as described at column 6, lines 4 to 25. Thus, Furie at al. does not teach or suggest the recitation of amended claim 1 that the first antibody and the second antibody are adsorbed on a carrier, or that the first antibody is adsorbed on a carrier, and the second antibody is adsorbed on a carrier dispersed in a solution or is dissolved in a solution.

Claims 1, 2, and 7-11 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Davalian et al. (U.S. 6,190,873). (Office action p. 8)

Reconsideration of the rejection is respectfully requested for the pending claims.

The Examiner cites Davalian for disclosing an immunoassay using specific binder pair members on a solid support (citing columns 26-30), stating that these involve antibodies specific for cyclosporin and antibodies to a cross-reactive material (citing columns 31-32, 34-35 and 49-55). The Examiner states that the relative affinities of the antibodies cannot be determined from the reference,

but "it would have been obvious to have provided the antibodies with the relative affinities as claimed and to adjust their relative concentrations in the assay dependent upon the level of expected interfering material and its cross-reactivity with the cyclosporin specific antibody as taught in the reference." The Examiner also implies that the limitations on the antibodies in claim 1 may be inherent in the reference.

However, Applicant submits that the antibodies in Davilian do **not** meet the limitations of claim 1 or 9.

The Davilian reference discloses antibodies against a conjugated cyclosporin A (column 24, lines 53 and ff.). The reference also discloses "antibodies which are capable of recognizing cross-reactive material in an assay for cyclosporin and thereby preventing the material from interfering with the assay" (column 31, lines 40-43). The reference further states: "Therefore, the antibodies will bind to the interfering cross-reactive material but will be substantially incapable of binding cyclosporin ...." (column 31, line 55). Note that this differs from the description of the "second antibody" of the present invention on page 12, lines 21-24, where the second antibody has affinity for **both** the target substance and the competitive substance, but that this recitation does not appear as a claim limitation in the present claims.

Therefore, Davilian's antibodies **do meet** limitations (ii) and (iii) of claim 1 or claim 9.

The Examiner implies that providing antibodies with the affinity limitations of claim 1 would have been obvious in Davilian (page 8, line 11, of the Office action). Applicant submits that there

is no basis for this assertion. In particular, additional steps are necessary in the monoclonal antibody selection process in order to meet these limitations. In fact, Davilian's disclosure at column 31, line 55, if applied to the first antibody, would **teach away** from claim limitation (i). There is no suggestion or motivation in the reference for specific selection of antibodies meeting the limitations of the present claims.

Further, Davalian et al. does not specifically teach that the first antibody and the second antibody are adsorbed on a carrier, or that the first antibody is adsorbed on a carrier, and the second antibody is adsorbed on a carrier in a solution or is dissolved in a solution. In this regard, Applicant notes that in the Examples of Davilian, the only assays given appear to be the "EMIT" assays in Examples 17 and 22. These do not involve adsorbing antibodies on a support.

Claims 1-4, 6-11, 13 and 14 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Halleen et al. et al. (U.S. 6,248,544).

(Office action p. 9)

Reconsideration of the rejection is respectfully requested for the pending claims.

The Examiner refers to Halleen's disclosure of a "TRAP 5b specific antibody [] used in combination with an antibody which recognizes both forms of enzymes, i.e., total TRAP" (column 6, lines 8-11). The Examiner also states that it would have been obvious to have provided antibodies with the relative affinities as instantly claimed "dependent upon the levels of expected isoforms."

However, Halleen's second antibody, which binds both forms of TRAP, is intended to bind both forms **well**, and there is no indication that this would meet limitation (iii) in claim 1. In addition, as with the Furie and Davilian references discussed above, there is no disclosure or suggestion for meeting limitations (i) and (iv) of claim 1 or 9.

The Examiner refers (page 9, line 15, of the Office action) to *In re Aller*, 105 USPQ 233. However, this court case deals with discovering optimal ranges for an adjustable variable, and does **not** indicate that it would be obvious to modify a prior art antibody selection process to select antibodies meeting certain criteria that are not, in fact, suggested in the prior art.

With regard to the "bonding" and "measuring" steps in claim 1, the Examiner refers generally to columns 6-9 of the reference. However, column 6, lines 8-15, reads as follows:

> However, it is preferrable [sic] that the TRAP 5b specific antibody is used in combination with an antibody, which recognizes both forms of enzymes, i.e. total TRAP. In that case the total TRAP of the body fluid may first be bound to the antibody recognizing both enzyme forms and then a labelled antibody, which is specific to TRAP 5b, but which does not react with TRAP 5a, is used to detect the bound TRAP 5b.

That is, the non-specific antibody (which recognizes both enzymes) is bound to the support at some point. However, the anti-TRAP 5b-specific antibody is "used to detect the bound TRAP 5b", that is, it is then reacted with the bound enzymes. The **specific antibody** (analogous to the first antibody), therefore, is **not** bound to the support (i.e., adsorbed on a carrier). This is clear from the disclosure in columns 6-7, and Example 2 in column 8, in which antibody O1A is adhered to

microtiter well (support), but **not** the TRAP 5b-specific antibody. However, claim 1 requires that the first antibody be adsorbed on a carrier.

Claims 1-4, 6-11, 13 and 14 are under 35 U.S.C. §103(a) as being unpatentable over Halleen et al. (U.S. 6,248,544) in view of Carlsson et al. (U.S. 6,737,278). (Office action p. 10)

Reconsideration of the rejection is respectfully requested for the pending claims.

Carlsson is cited for a method for performing immunoassays on a flow matrix. The Examiner states that it would have been obvious "to have used the flow matrix method and kit of Carlsson for the determinations of the isoforms of tartrate resistant acid phosphatase in Halleen et al. in view of the direct suggestion in Carlsson et al. to use the method and kit for determination of heteroforms having or lacking a binding site for a particular monoclonal antibody."

Carlsson discloses a ligand binding assay involving a flow matrix with a sample application zone (ASZ) for a binding reactant, and a detection zone (DZ) exhibiting another binding reactant (capturer) firmly anchored to the matrix. Carlsson's apparatus is a **flow matrix** apparatus (column 4, line 51), and in general, analytes flowing in it are "retarded/separated" (column 3, line 53). In Carlsson's apparatus, the substance is assayed (i.e., level measured) while it is in the DZ portion of the apparatus.

Applicant respectfully submits that it is unclear in the rejection how Carlsson's apparatus would be applicable to Halleen's assay, and how the references are being combined. Moreover, even

if Carlsson's apparatus were somehow used with Halleen's two antibodies, it is not clear that this would meet the limitation of claim 1 wherein the first antibody and the second antibody are adsorbed on a carrier, or that the first antibody is adsorbed on a carrier, and the second antibody is adsorbed on a carrier in a solution or is dissolved in a solution.

In addition, as noted above for the rejection over Halleen, Halleen does not disclose or suggest antibodies meeting limitations (i), (iii) and (iv) of the present claims.

The pending claims are therefore not obvious over Halleen and Carlsson, taken separately or in combination.

If, for any reason, it is felt that this application is not now in condition for allowance, the Examiner is requested to contact the applicant's undersigned agent at the telephone number indicated below to arrange for an interview to expedite the disposition of this case.

In the event that this paper is not timely filed, the applicant respectfully petitions for an appropriate extension of time. Please charge any fees for such an extension of time and any other fees which may be due with respect to this paper, to Deposit Account No. 01-2340.

Respectfully submitted,

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Enclosure: Petition for Extension of Time

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